



## Antibiotics, Vaginal Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
clindamycin vaginal 2% cream (Cleocin®) <sup>1</sup>	generic	Treatment of bacterial vaginosis in non-pregnant women and pregnant women during the second and third trimester
clindamycin vaginal 2% cream (Clindesse) <sup>2</sup>	Perrigo	Single dose treatment of bacterial vaginosis for non-pregnant women
clindamycin vaginal ovules (Cleocin®) <sup>3</sup>	Pfizer	Three-day treatment of bacterial vaginosis in non-pregnant women
metronidazole vaginal 0.75% gel (MetroGel-Vaginal®) <sup>4</sup>	generic	Treatment of bacterial vaginosis in non-pregnant women
metronidazole vaginal 0.75% gel (Vandazole®) <sup>5</sup>	Upsher-Smith	Treatment of bacterial vaginosis in non-pregnant women
metronidazole vaginal 1.3% gel (Nuversa™) <sup>6</sup>	Actavis	Treatment of bacterial vaginosis in non-pregnant women

## OVERVIEW

Bacterial vaginosis is a condition in women that is characterized by thin, grayish vaginal discharge with a foul-smelling odor, especially after intercourse.<sup>7</sup> Bacterial vaginosis is often asymptomatic and results from an overgrowth of bacteria in the vagina caused by a disruption of the vaginal environment. This disruption can be attributed to a number of factors, including douching and sexual relations. The polymicrobial clinical syndrome results from the replacement of normal *Lactobacillus* sp in the vagina with high concentrations of anaerobic bacteria, such as *Gardnerella vaginalis* and *Mycoplasma hominis*.

In clinical practice, bacterial vaginosis is diagnosed using the Amsel's criteria defined by thin, white, yellow, homogeneous discharge, contain clue cells on microscopic examination, pH of vaginal fluid greater than 4.5, and release of a fishy odor on adding alkali -10% potassium hydroxide (KOH) solution (whiff test).<sup>8</sup> At least 3 of the 4 criteria should be present for a confirmed diagnosis.<sup>9</sup> Gram stain results consistent with a diagnosis of bacterial vaginosis include markedly reduced or absent *Lactobacillus* morphology, predominance of *Gardnerella* morphotype, and absent or few white blood cells. Other pathogens commonly associated with vulvovaginitis include *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus; these should be ruled out.

The goal in treating bacterial vaginosis is to reduce the number of pathogenic bacteria in the vagina allowing the normal bacteria to flourish.<sup>10</sup>

Treatment benefits include relief from vaginal symptoms and signs of infection and reducing the risk of infectious complications after abortion or hysterectomy.<sup>11</sup> Additionally, other potential benefits include a reduction in risk of other infections (Human Immunodeficiency Virus [HIV] and other sexually-transmitted diseases). Bacterial vaginosis in pregnancy has been associated with adverse pregnancy outcomes including premature rupture of membranes, preterm labor, preterm birth, intra-amniotic infections, and postpartum endometritis. Some studies have found that treatment of pregnant women with bacterial vaginosis who are at high risk for preterm delivery (those with a history of premature delivery) might reduce the risk of prematurity.<sup>12,13,14</sup> All women who have symptomatic disease require treatment.

According to the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases (STD) 2015 Treatment Guidelines, the recommended regimens for the treatment of bacterial vaginosis in non-pregnant women include oral metronidazole 500 mg twice daily for 7 days, metronidazole gel 0.75% given as 1 full applicator intravaginally once daily for 5 days, or clindamycin 2% cream given as 1 full applicator intravaginally at bedtime for 7 days.<sup>15</sup> Patients should be advised to avoid consuming alcohol during treatment with metronidazole and for 24 hours thereafter. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use. Topical clindamycin preparations should be used in pregnancy only if clearly indicated.

Alternative regimens include oral clindamycin 300 mg twice daily for 7 days, clindamycin ovules 100 mg intravaginally once at bedtime for 3 days, oral tinidazole (Tindamax) 2 g once daily for 2 days, or oral tinidazole 1 g once daily for 5 days.<sup>16</sup> Oral metronidazole 2 g as a single dose has the lowest efficacy for bacterial vaginosis and is no longer recommended as an alternative regimen by the CDC. Additionally, metronidazole ER (Flagyl ER®) 750 mg oral tablets once daily for 7 days, metronidazole 1.3% gel (Nuversa) as a single dose intravaginally, clindamycin phosphate 2% cream (Clindesse) as a single dose intravaginally are FDA-approved treatments for bacterial vaginosis.

## PHARMACOLOGY<sup>17,18,19,20,21,22</sup>

Clindamycin binds to the 50S ribosomal subunits of the bacteria, which affects the process of peptide chain initiation. As with lincomycin, antibacterial activity results from inhibition of protein synthesis. Clindamycin is either bacteriostatic or bactericidal, depending on its concentration at the site of action and on the specific susceptibility of the organism being treated. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin is active against a wide range of aerobic gram-positive cocci, as well as several anaerobic gram-negative and gram-positive organisms. Species of streptococci (except for enterococci) and staphylococci are extremely susceptible. Most anaerobes, both gram-positive and gram-negative, are also susceptible. Clindamycin is a well-known cause of pseudomembranous colitis, possibly due to overgrowth of *Clostridium difficile*. Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. Antibiotic resistance among anaerobic bacteria has developed following intravaginal clindamycin therapy and persisted for 90 days after treatment in one small study.<sup>23</sup>

Metronidazole is a synthetic antibacterial and antiprotozoal agent that belongs to the nitroimidazole class. It is effective therapy against protozoa, such as *Trichomonas vaginalis*, amebiasis, and giardiasis. In addition, it is one of the most effective drugs available against anaerobic bacterial infections.

Metronidazole is amebicidal, bactericidal, and trichomonacidal. Unionized metronidazole is readily taken up by anaerobic organisms and cells. Its selectivity for anaerobic bacteria is a result of the ability of these organisms to reduce metronidazole to its active form intracellularly. The electron transport proteins necessary for this reaction are found only in anaerobic bacteria. Reduced metronidazole then disrupts DNA's helical structure, thereby inhibiting bacterial nucleic acid synthesis. This eventually results in bacterial cell death. Metronidazole is equally effective against dividing and nondividing cells.

Metronidazole's spectrum of activity includes protozoa and obligate anaerobes including: *Bacteroides* group, *Fusobacterium*, *Veillonella*, the *Clostridium* group (including *C. difficile* and *C. perfringens*), *Eubacterium*, *Peptococcus*, and *Peptostreptococcus*. It is effective against *B. fragilis* isolates that are resistant to clindamycin. It is not effective against the common aerobes but is active against the aerobe *Gardnerella vaginalis*. The protozoan coverage of metronidazole includes *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas vaginalis*. As with most antimicrobials, local resistance patterns may also affect spectrum.

## PHARMACOKINETICS<sup>24,25,26,27,28,29</sup>

Clindamycin intravaginal products (Cleocin) are systemically absorbed, but systemic levels are significantly lower than those following oral or intravenous administration. Metronidazole (MetroGel-Vaginal, Nuversa, Vandazole) systemic absorption is minimal.

## CONTRAINDICATIONS/WARNINGS<sup>30,31,32,33,34,35</sup>

Clindamycin (Cleocin) is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of the vaginal creams. Clindamycin is also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

The patient should also be advised that clindamycin cream contains mineral oil that may weaken latex or rubber products, such as condoms or vaginal contraceptive diaphragms. Therefore, use of such products within 3 to 5 days following treatment with clindamycin vaginal cream 2% is not recommended.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally- and parenterally-administered clindamycin has been associated with severe colitis which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally- and parenterally-administered clindamycin, as well as with topical formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of clindamycin, even though there is minimal systemic absorption of clindamycin from the vagina with administration of vaginal creams. Discontinue use and evaluate if diarrhea occurs.

Metronidazole vaginal gel (MetroGel-Vaginal, Nuversa, Vandazole) is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives. Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral or intravenous metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy. Metronidazole vaginal gel should be administered with caution to patients with central nervous system diseases.

Metronidazole has been shown to be carcinogenic in mice and rats; therefore, unnecessary use should be avoided. There could also be interference with certain serum chemistry laboratory values, including aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Assays affected involve enzymatic coupling of the assay to the oxidation-reduction of nicotinamide-adenine dinucleotides (NAD + NADH). Interference is due to

the interference in the absorbance peak of NADH (340 nm) by metronidazole. Consequently, values may be depressed and values as low as zero may be reported.

Psychotic reactions have been reported in alcoholic patients who were using oral metronidazole and disulfiram concurrently. Metronidazole vaginal gel should not be administered to patients who have taken disulfiram within the last 2 weeks. Alcohol should not be consumed during metronidazole use and for at least 3 days following treatment.

## DRUG INTERACTIONS<sup>36,37,38,39,40,41</sup>

The intravaginal administration of clindamycin (Cleocin, Clindesse) results in relatively lower systemic concentrations compared to oral formulations. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

The intravaginal administration of metronidazole vaginal gel (MetroGel-Vaginal, Nuversa, Vandazole) results in relatively lower systemic metronidazole concentrations compared to that following a 500 mg metronidazole oral dose. Drug interactions have been identified with oral metronidazole and include the following: warfarin (potential to increase INR and anticoagulant effects); lithium (potential to elevate serum lithium levels); and cimetidine (may decrease plasma clearance and increase half-life of metronidazole).

## ADVERSE EFFECTS<sup>42,43,44,45,46,47</sup>

Drug	Fungal vaginosis	Vulvovaginal pruritus	Headache	GI Discomfort
clindamycin 2% cream (Cleocin) 3-day treatment	7.7	<1	<1	<1
clindamycin 2% cream (Cleocin) 7-day treatment	10.4 (non-pregnant) 13.3 (pregnant)	<1	<1	<1
clindamycin 2% cream (Clindesse)	14	nr	7	nr
clindamycin ovule (Cleocin)	1.5	reported	reported	reported
metronidazole 0.75% gel (MetroGel-Vaginal)	6-10	9	5	7
metronidazole 0.75% gel (Vandazole)	12	6	7	1-5
metronidazole vaginal 1.3% gel (Nuversa)	5.6	1.6	2.2	nr

Adverse effects data are reported from product information as percentage occurrence and, therefore, cannot be considered comparative or all inclusive. Incidences for placebo group are shown in parentheses. nr = not reported.

## SPECIAL POPULATIONS<sup>48,49,50,51,52,53</sup>

### Pediatrics

The safety and efficacy of clindamycin vaginal cream (Cleocin) and vaginal ovules (Cleocin) and metronidazole vaginal gel (MetroGel-Vaginal, Nuessa, Vandazole) in the treatment of bacterial vaginosis in post-menarchal females have been established on the extrapolation of clinical trial data from adult women.

The safety and efficacy of clindamycin vaginal products and metronidazole vaginal gel in premenarchal females have not been established.

### Pregnancy

Bacterial vaginosis has been associated with adverse pregnancy outcomes, such as premature rupture of the membranes, chorioamnionitis, preterm labor, preterm birth, intra-amniotic infection, postpartum endometritis, and postcesarean wound infection.

Clindamycin and metronidazole are Pregnancy Category B. Clindamycin 2% may be used in second and third trimester of pregnancy for the treatment of bacterial vaginosis. The 2015 CDC STD treatment guidelines recommend that all symptomatic pregnant women be treated.<sup>54</sup> Literature does not support superiority of oral regimens over intravaginal regimens; pregnant women can be treated with either oral or intravaginal regimens.

The updated 2015 CDC STD treatment guidelines found mixed results when looking at whether to treat asymptomatic women both at high risk for preterm birth or not at high risk for preterm birth.<sup>55</sup> Treatment of asymptomatic bacterial vaginosis among pregnant women who are at high risk for preterm delivery (e.g., those with a previous preterm birth) has been evaluated by several studies with varying results. A review of studies regarding whether treatment of asymptomatic bacterial vaginosis among pregnant women who are at low risk for preterm delivery reduces adverse outcomes of pregnancy also found varying results. Therefore, evidence is insufficient to recommend routine screening for bacterial vaginosis in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth.

A systematic review evaluated 21 clinical trials (n=7,847) investigating antibiotic therapy for eradication of bacterial vaginosis during pregnancy.<sup>56</sup> Antibiotic therapy was effective in eradicating bacterial vaginosis during pregnancy (average risk ratio [RR], 0.42; 95% confidence interval [CI], 0.31 to 0.56). Antibiotic therapy also was found to reduce the risk of late miscarriage (RR, 0.2; 95% CI, 0.05 to 0.76). However, treatment did not reduce the risk of preterm birth (PTB) before 37 weeks gestation (RR, 0.88; 95% CI, 0.71 to 1.09), nor did it reduce the risk of preterm prelabor rupture of membranes (RR, 0.74; 95% CI, 0.3 to 1.84). Treatment earlier than 20 weeks gestation was not found to reduce the risk of PTB less than 37 weeks (RR, 0.85; 95% CI, 0.62 to 1.17). The authors concluded that treatment of bacterial vaginosis with antibiotics can eradicate bacterial vaginosis in pregnancy, but the overall risk of PTB was not significantly reduced. The use of intravaginal clindamycin during pregnancy to reduce preterm birth and treat asymptomatic bacterial vaginosis has been reported with mixed results. In a trial with 409 pregnant women between 13 and 20 weeks gestation with abnormal genital tract flora, clindamycin 2% intravaginally for 3 days significantly reduced the incidence of preterm birth compared to placebo (4% versus 10%; p<0.03).<sup>57</sup>

In 3 other trials, intravaginal clindamycin cream was administered at 14 to 32 weeks' gestation; an increase in adverse events, such as low birth weight and neonatal infections, was observed in infants.<sup>58,59,60</sup> Potentially negative changes in genital tract flora following administration of vaginal clindamycin have been observed in a clinical trial with pregnant women.<sup>61</sup> Other trials have not shown benefit in reducing preterm birth after treatment of asymptomatic bacterial vaginosis with clindamycin 2%.<sup>62,63,64</sup>

## Renal and Hepatic Impairment

Patients with severe hepatic disease metabolize metronidazole slowly. This results in the accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, metronidazole vaginal gel should be administered cautiously.

## DOSAGES<sup>65,66,67,68,69,70</sup>

Drug	FDA-Approved Dosage for Bacterial Vaginosis	CDC Recommended Dosage for Bacterial Vaginosis <sup>71</sup>	Availability
clindamycin vaginal 2% cream (Cleocin)	1 applicatorful (~5 gm, equivalent to 100 mg clindamycin) intravaginally, preferably at bedtime, for 3 or 7 consecutive days in non-pregnant patients and for 7 consecutive days in pregnant patients	1 applicatorful (100 mg clindamycin/ 5 g cream) intravaginally at bedtime for 7 days for non-pregnant women	40 gm tube with 7 applicators
clindamycin vaginal 2% cream (Clindesse)	1 applicatorful of cream once intravaginally at any time of day	Not mentioned by CDC	Single dose prefilled disposable applicator
clindamycin vaginal ovules (Cleocin)	1 ovule (containing clindamycin phosphate equivalent to 100 mg clindamycin per 2.5 g suppository) intravaginally per day, preferably at bedtime, for 3 consecutive days	As an alternative to first-line therapies, 1 ovule (100 mg clindamycin) inserted intravaginally at bedtime for 3 days for non-pregnant women	Three 100 mg ovules plus 1 applicator
metronidazole 0.75% gel (MetroGel-Vaginal)	1 applicatorful (~5 gm containing ~37.5 mg of metronidazole) intravaginally once or twice a day for 5 days For once daily dosing, metronidazole vaginal gel should be administered at bedtime	1 applicatorful (5 g of 0.75% metronidazole gel) intravaginally once daily for 5 days for non-pregnant women	70 gm tube with 5 applicators
metronidazole 0.75% gel (Vandazole)	1 applicatorful (~5 gm containing ~37.5 mg of metronidazole) intravaginally once or twice a day for 5 days For once daily dosing, metronidazole vaginal gel should be administered at bedtime	1 applicatorful (5 g of 0.75% metronidazole gel) intravaginally once daily for 5 days for non-pregnant women	70 gm tube with 5 applicators
metronidazole 1.3% gel (Nuversa)	1 applicatorful (5 gm containing 65 mg of metronidazole) intravaginally at bedtime as a single dose	Not mentioned by CDC	Single dose prefilled disposable applicator



## CLINICAL TRIALS

### Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved vaginal use of all drugs in this class. Randomized controlled comparative trials for bacterial vaginosis are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to limited availability of data, unblinded, single-blinded, and phase 2 studies have been included.

### **clindamycin ovule (Cleocin) versus clindamycin 2% cream**

In a prospective investigator-blinded trial, the efficacy and safety of a 3-day regimen of clindamycin vaginal ovules and a 7-day regimen of clindamycin vaginal cream for the treatment of bacterial vaginosis were evaluated.<sup>72</sup> A total of 384 women with a clinical diagnosis of bacterial vaginosis were enrolled. Primary efficacy endpoints were a resolution of 2 of 3 diagnostic criteria at the first follow-up visit and all 3 diagnostic criteria at the second. Cure rates were similar between the treatment groups (ovule 53.7% versus cream 47.8%; 95% CI, -4.1 -16; p=0.2471). Reports of vulvovaginal pruritus were similar in both groups. This study lacked double-blinding. One of the 5 authors was an employee of the manufacturer of Cleocin ovules.

### **clindamycin 2% cream versus clindamycin cream (Clindesse)**

A multicenter, randomized, single-blind, parallel-group study enrolled patients (n=540) with bacterial vaginosis infection. Treatment was either a single intravaginal dose of Clindesse or 7 daily doses of Cleocin cream.<sup>73</sup> Efficacy and safety were assessed 21 to 30 days after treatment. Efficacy endpoints were Investigator Cure, Clinical Cure, Nugent Cure, and Therapeutic Cure. Adverse events were also monitored during the study. There were no significant differences in cure rates between the 2 treated groups. There were no significant differences in the incidence of adverse events. It was concluded that a single dose of Clindesse vaginal cream is equivalent in both safety and efficacy to a 7-dose regimen of clindamycin vaginal cream for the treatment of bacterial vaginosis.

## **clindamycin 2% cream versus oral metronidazole (Flagyl)**

In a prospective, double-blind trial, clindamycin vaginal cream was compared to oral metronidazole in the treatment of bacterial vaginosis in 60 women.<sup>74</sup> A total of 46 women completed the trial. Patients were randomized to clindamycin 2% vaginal cream at bedtime for 7 nights with placebo oral tablets (n=23) or oral metronidazole 500 mg twice daily for 7 days with nightly placebo vaginal cream for 7 nights (n=23). Cure rates and adverse events were comparable. In the clindamycin group, 97% of the patients had improvement or cure at the first follow-up visit versus 83% of those taking oral metronidazole (p=NS). This study had a completion rate of 76%.

Another randomized, double-blind study enrolled 48 women with symptomatic bacterial vaginosis to evaluate the safety and efficacy of clindamycin 2% vaginal cream daily or oral metronidazole 500 mg twice daily for 7 days.<sup>75</sup> After completion of therapy, there was no significant difference in cure rates (clindamycin 72% versus metronidazole 87%). At another follow-up visit 1 month later, 61% of the patients in each group were still cured. Adverse effects were similar in both groups.

## **clindamycin 2% cream versus metronidazole 0.75% gel versus oral metronidazole**

A total of 101 women with bacterial vaginosis were enrolled in a trial comparing oral metronidazole 500 mg twice daily for 7 days, clindamycin 2% vaginal cream daily for 7 days, and metronidazole 0.75% vaginal gel twice daily for 5 days.<sup>76</sup> The efficacy of the 3 treatments was evaluated by cure rate using clinical and laboratory tests, including vaginal saline wet prep and potassium hydroxide microscopic examinations, Gram's stain, pH and DNA probe tests for *Gardnerella vaginalis* and *Candida* species after 7 to 14 days following treatment. There were no statistically significant differences in cure rates for oral metronidazole (84.2%), metronidazole vaginal gel (75%), or clindamycin vaginal cream (86.2%). Cure rates were lower based on DNA testing, indicating that *Gardnerella vaginalis* may remain after a clinical cure. Post-treatment vulvovaginal candidiasis was experienced by 12.5% of subjects treated with oral metronidazole, 14.8% of subjects treated with clindamycin vaginal cream, and 30.4% of subjects treated with metronidazole vaginal gel.

## **metronidazole 1.3% gel versus metronidazole 0.75% gel**

A total of 255 women with a diagnosis of bacterial vaginosis were enrolled in a phase 2, randomized, dose-ranging study and assigned to either metronidazole 1.3% gel once daily for 1, 3, or 5 days or metronidazole 0.75% gel once daily for 5 days.<sup>77</sup> The therapeutic cure rate (requiring clinical and bacteriological cure) was higher in the metronidazole 1.3% one day (30.2%), 3 day (25%), and 5 day (32.7%) regimens as compared to the metronidazole 0.75% group (20.4%). There were no clinically significant differences observed in adverse effects across treatment groups. Metronidazole vaginal gel 1.3% applied as a single dose showed similar efficacy, safety, and tolerability as metronidazole 0.75% applied daily for 5 days.

## SUMMARY

According to the 2015 CDC treatment guidelines for sexually transmitted diseases, the recommended regimens for the treatment of bacterial vaginosis in non-pregnant women include oral metronidazole 500 mg twice daily for 7 days, metronidazole gel 0.75% given as 1 full applicator intravaginally once daily for 5 days, or clindamycin 2% cream given as 1 full applicator intravaginally at bedtime for 7 days. Very little good quality direct comparative data are available. Shorter course therapy for bacterial vaginosis in non-pregnant women is available as 3-day clindamycin ovules (Cleocin), single dose clindamycin 2% cream (Clindesse), and single dose metronidazole 1.3% gel (Nuessa).

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